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10/596,198	03/09/2007	**Inderjit Singh**	MESC:013US	3351

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EXAMINER	
AUDET, MAURY A	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,198	SINGH, INDERJIT	
	Examiner	Art Unit	
	MAURY AUDET	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46 and 48-61* is/are pending in the application.

4a) Of the above claim(s) *1-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-46 and 48-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/2/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/19/09,12/8/08,5/10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claims 33-46 and 48-61 in the reply filed on 11/17/09 is acknowledged (composition and method of use to treat diabetes; it is noted that the method of use was inadvertently grouped with the product claims; but the Examiner will go forward with examination of both in the interests of advancing prosecution).

Claims 1-32 are withdrawn as being drawn to non-elected subject matter.

Independent claim 33 is drawn to a composition comprising two genus classes of molecules:

(a) ANY glutathione donor (with Markush group examples in e.g. dependent claim 36);

PLUS

(b) a Markush group comprising:

i. 3 specific compounds;

ii. a genus 4th compound (ANY inhibitor of HMG-CoA), &

iii. ANY derivative of the compounds of i. or ii. [BUT NOT (a) it is appears]

While independent claim 48 is drawn to a composition comprising the following two genus classes of molecules:

(a) ANY glutathione donor (with Markush group examples in e.g. dependent claim 36);

PLUS

(b) ANY statin – WHICH ARE KNOWN HMG-CoA INHIBITORS (see e.g.

OR

(c) ANY derivative of the (a) or (b) [Versus claim 33, not drawn to any glutathione donor].

It is noted that the Examiner did not require a single compound from (a) and (b) be elected as the invention (e.g. independent and distinct combination). Or even a species election thereof. The Examiner went forward with the search and applied the art below with the understanding that any art on any 1 compound (combination) of all the potential compounds of (a) and (b), would render obvious any other compounds to fall within said genus and/or Markush group; absent evidence to the contrary. As genuses/Markush groups are deemed to all contain the same desired structure and/or properties, to be claimed collectively – since, were this not the case, any combinations falling outside this scope would constitute an independent and distinct invention, to which art on one would not read on the latter. If the latter be the case, Applicant is advised to inform the Office in the next response and proactively elect (and amend the claims to) a single combination as the invention (not species), to which this individual and distinct invention would then be searched. However, any art found thereon, even if new, would be applied as a Final Rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 33-36, 39, 41-42 rejected under 35 U.S.C. 102(b) as being anticipated by Kindness et al. (US 2002/0132781 A1; published 9/19/02, > 1 yr. before Applicant's 12/23/03 priority date).

Kindness et al. teach the combination of (a) glutathione donors such as N-acetyl-cysteine (NAC) and (b) ANY HMG-CoA inhibitor:

> [0043] No patent or literature suggests the preferred embodiment that a COX-2 inhibitor be combined with **an HMG-CoA inhibitor** to retard cancer and be **further combined with** a glutathione**-cycle enhancing compound** such as cystine, cysteine, or **N-acetyl-cysteine, also called NAC**, to improve immune system competency to further retard cancer.

; wherein the HMG-CoA inhibitor is selected from the group consisting of (Claim 1):

> "particularly those known as statins, including lovastatin, simvastatin, pravastatin, compactin, atorvastatin calcium, cerivastatin sodium, fluvastatin sodium, and cholestin, to initially achieve a therapeutically effective change in cholesterol"

> [0057] ...atorvastatin calcium, marketed under the name LIPITOR by Parke-Davis, and described, among other places, in U.S. Pat. No. 5,273,995.

Thus, Kindness et al. expressly teach the combination of glutathione donors such as NAC and HMG-CoA inhibitors or Markush group compounds related thereto (see also entire document).

Note 102 to 103 transition: Although Kindness teach the above combination for use in cancer - rather than diabetes (presently claimed method) - both classes of compounds presently claimed for combination have been found to be art-recognized for their use in diabetic treatment. And thus, even if not expressly combined together, constitute obvious combinations for their known use, as taken up under 35 USC 103 below, regarding the

method of use, as well as other combining other related compounds in these 2 classes claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 33-46 and 48-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kindness et al. (US 2002/0132781 A1) in view of I. Fantus (US 6258848 B1) or Richardson et al. (US 2003/0077335 A1) and II. Mach (US 2003/0060502) or Timmons et al. (US 6660300).

Kindness et al., as discussed above, teach the product combination of (a) glutathione donors such as N-acetyl-cysteine (NAC) and (b) ANY HMG-CoA inhibitor:

> [0043] No patent or literature suggests the preferred embodiment that a COX-2 inhibitor be combined with **an** HMG-CoA **inhibitor** to retard cancer and be **further combined with** a glutathione**-cycle enhancing compound** such as cystine, cysteine, or **N-acetyl-cysteine, also called NAC**, to improve immune system competency to further retard cancer.

; wherein (Claim 1) the **HMG-CoA inhibitor is selected from the group consisting of**:

> "particularly those known as statins, including lovastatin, simvastatin, pravastatin, compactin, atorvastatin calcium, cerivastatin sodium, fluvastatin sodium, and cholestin, to initially achieve a therapeutically effective change in cholesterol"

> [0057] ...atorvastatin calcium, marketed under the name LIPITOR by Parke-Davis, and described, among other places, in U.S. Pat. No. 5,273,995.

Thus, Kindness et al. expressly teach the combination of glutathione donors such as NAC and HMG-CoA inhibitors or Markush group compounds related thereto (see also entire document). However, Kindness et al. does not expressly teach the use of the combination for treating diabetes.

I. (a) glutathione donors such as N-acetyl-cysteine (NAC) in diabetic treatment

A. Fantus teach the use of the (a) glutathione donor N-acetyl-cysteine (NAC) for the treatment of diabetes (see title, entire document).

B. Richardson et al. teach, as titled, the beneficial use of the (a) glutathione donor N-acetyl-cysteine (NAC) for the treatment of diabetes (see title; para's 437, 440; entire document):

> Formulations for the prevention and treatment of insulin resistance and type 2 diabetes mellitus

> [0437] Cysteine is the essential sulfur-containing amino acid in GSH. NAC increases systemic GSH by supplying the necessary cysteine intracellularly. GSH and glutathione peroxidase levels are notably reduced in progressive insulin resistance and type 2 diabetes. The deficiencies and the associated peroxide-mediated damage to cell membranes may appear early in the progressive insulin resistance and type 2 diabetes, before the development of secondary complications. Additionally, GSH counterbalances the effects of ICAM-1, one of the most important intercellular adhesion molecules involved with the atherogenesis associated with insulin resistance syndrome and type 2 diabetes. GSH similarly reduces thrombin activation, which results from hyperglycemia.

> [0440] The antioxidant abilities of NAC and other elements of this invention, have the potential to delay the onset and delay the progression of "type 1.5 diabetes". In the latter, ROS destroy pancreatic .beta.-cells. This .beta.-cells destruction results in the addition of insulin-dependent (type 1) diabetes mellitus clinical findings to those already existing from type 2 diabetes. Activation of NFkappaB by ROS-induced release of mitochondrial cytochrome C seems to be the key cellular signal in initiating a cascade of events leading to .beta.-cell death in this scenario. Thus, enhancement of pancreatic GSH (via oral administration of the prodrug NAC or .alpha.-lipoic acid)--a key intracellular regulator of NF-kappaB--affords protection against the insidious onset of "type 1.5 diabetes". In this context, supplementation with 500 mg/kg of NAC as a GSH precursor, has been shown to inhibit alloxan-induced NFkappaB activation, and subsequently reduce hyperglycemia. By inference, NFkappaB activation by ROS (via the mitochondria) may initiate a sequence of events eventually leading to type 1 diabetes, by way of "type 1.5 diabetes": In one study, inhibition of NF-kappaB activation by NAC has been shown to attenuate the severity of type 1 diabetes.

II. (b) class of compounds related to HMG-CoA reductase inhibitors, such as statins (e.g. atorvastatin/LIPITOR) in diabetic treatment

A. Mach, as titled, teach the use of statins, such as atorvastatin/Lipitor, to treat diabetes (title; Claim 18; entire document):

> "Treatment of diabetes with statins (HMG-CoA reductase inhibitors)"
>
> 18. The method of any one of claims 1 to 4, wherein said statin is Compactin, Atorvastatin, Lovastatin, Pravastatin, Fluvastatin, Mevastatin, Cerivastatin, Rosuvastatin or Simvastatin.

B. Timmons et al. teach the use of HMG-CoA inhibitors such as atorvastatin/Lipitor in the treatment of diabetes (e.g. Claims 25, 46; entire document):

> 25. The method for treating diabetes as defined in claim 21 wherein said hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.
> 46. The method of treating diabetes as defined in claim 42 wherein said hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

III. PREDICTABILITY OF LIKE-KIND COMBINATIONS/KNOWN USE IN DIABETIC TREATMENT

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use any (a) glutathione donor (e.g. NAC) in combination with (b) another compound selected from a class of Markush group compounds related to HMG-CoA reductase inhibitors (e.g. statins such as atorvastatin) and use the same to treat diabetes in Kindness et al., because Kindness et al. expressly teaches a combination composition of the glutathione donor NAC and HMG-CoA reductase inhibitors, such as the preferred atorvastatin. Furthermore:

i) Fantus and X each expressly teach that the former class (a) compounds are art-recognized for their use in diabetic therapy; and

ii) Mach and Timmons et al. each expressly teach that the latter class (b) compounds are art-recognized for their use in diabetic therapy

Thus, even if not expressly combined together, combining classes of compounds from (a) and (b) for their known use in diabetic therapy would have had a predictable outcome of being therapeutic, the selection of a compound from either related Markush group class merely constituting a matter of routine optimization by the skilled artisan depending on the desired results - absence evidence to the contrary of some unexpected result by one or more specific combinations, and specific range amounts thereof.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 33-46 and 48-61 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-47 of U.S. Patent No. 7049058 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '058 patent is drawn to methods of use, but they nevertheless are drawn to compositions comprising presently claimed genus/species (e.g. NAC (present species of element (a) glutathione donor) in combination with AICAR (present species of element (b)).

Claim Rejections - 35 USC § 112 2nd

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-46 and 48-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. In e.g. claim 1, what is meant by the compound name "3-hydroxy-3-**methylgluatryl**-coenzymeA (HMG-CoA) reducatase inhibitor"? Is methylgluatryl misspelled? Is the correct spelling **methylglutaryl**? Or is this a new type of HMG-CoA reductase inhibitor compound? **The specification bears the same spelling or misspelling**. Since HMG is a known acronym, Applicant has support for correcting this spelling to methylglutaryl, if this is in fact the intended compound. A search thereof is not possible until corrected.

2. In e.g. claim 1, what is meant by "3-hydroxy-3-methylgluatryl-coenzymeA (HMG-CoA) reducatase **inhibitor**"? What is the metes and bounds of what falls into the category of an HMG-CoA reducatase inhibitor? The specification (para 19 and 100) lists that a very broad subgenus species of compounds, STATINS, fall within this genus. But this is the only species cited:

> [0019]
> []
> The HMG-CoA reductase inhibitor can be a statin. Non-limiting examples of statins that can be used with the present invention include atorvastatin, lovastatin, rosuvastatin, fluvastatin, pravastatin, simvastatin, or cerivastatin, or derivatives thereof.

> [0100] HMG-CoA reductase catalyzes the conversion of hydroxymethylglutaryl-CoA to mevalonic acid, an early rate-limiting step in cholesterol biosynthesis. Particular HMG-CoA reductase inhibitors that can be used with the present invention include statins. In

> clinical studies, statins reduce total cholesterol, LDL cholesterol, apolipoprotein B and triglyceride levels. Statins can also increase HDL levels. Statins that are contemplated as being useful with the present invention include, but are not limited to, atorvastatin, lovastatin, rosuvastatin, fluvastatin, pravastatin, simvastatin, and cerivastatin. The chemical formulas for these statins include:

What other subgenuses and/or species are intended to be embodied by this label "inhibitor"? Until the metes and bounds of this definition are clarified *OR Applicant amends the claims to be drawn only to ANY statin*; the metes and bounds of "inhibitor" are infinite, and thus indefinite. [A 35 USC 112 1st Written Description Rejection has not been made here; as what falls into this genus is deemed known; but nevertheless indefinite until Applicant reconciles his definition with a source in the art identifying what else falls within the metes and bounds of the term 'inhibitor'].

NOTE: The phrase "or [ANY] derivative thereof", following the Markush group of 5 molecule genuses that can be selected from element (b), for the composition, is deemed definite; based on it's structure + function specification definition requirement:

> [0025] Non limiting examples of derivatives include chemically modified compounds of a glutathione donor, AICAR, an AMP-activated kinase (e.g., an HMG-CoA reductase inhibitor), D-PDMP, and/or Miglustat **that still retain the desired effects on treating or preventing inflammatory diseases or conditions.** Such derivatives may have the addition, removal, or substitution of one or more chemical moieties on the parent molecule. Non-limiting examples of modifications may include the addition or removal of lower alkanes such as methyl, ethyl, propyl, or substituted lower alkanes such as hydroxymethyl or aminomethyl groups; carboxyl groups and carbonyl groups; hydroxyls; nitro, amino, amide, and azo groups; sulfate, sulfonate, sulfono, sulfhydryl, sulfonyl, sulfoxido, phosphate, phosphono, phosphoryl groups, and halide substituents. Additional modifications can include an addition or a deletion of one or more atoms of the atomic framework, for example, substitution of an ethyl by a propyl; substitution of a phenyl by a larger or smaller aromatic group. Alternatively, in a cyclic or bicyclic structure, hetero atoms such as N, S, or O can be substituted into the structure instead of a carbon atom. Such a derivative may be prepared by any method known to those of skill in the art. The properties of such derivatives may be assayed for their desired properties by any means described herein or known to those of skill in the art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 1/4/2010

/Maury Audet/
Primary Examiner, Art Unit 1654